FLOATING MICROFLUIDIC GRADIENTS
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ABSTRACT
We propose a concept for rapid generation of tunable, shear-free, mobile gradients in open space which we define as floating gradient. A microfluidic probe with 4 apertures arranged at the corners of a virtual square, two for injecting fluids and two for aspiration. The simultaneous injection from two apertures results to a head-to-head flow at the center of the MFP, and the formation of a stagnation point, while aspiration by the two other apertures results in hydrodynamic confinement of the injected streams, forming a quadrupole-like microfluidic field. The two injected streams are the source and sink, respectively, and a gradient is formed across the shear-free, stagnation point. We show that the gradient is formed rapidly, can be tuned by changing the aspiration flow rate, and can be moved either hydrodynamically by changing the flow ratio between the two aspiration apertures and/or two injection apertures, or can be moved by physically displacing the microfluidic probe. We expect the floating gradient concept to be useful for surface patterning and cell studies.

KEYWORDS: Stagnation point, Concentration gradients, Microfluidic probe

INTRODUCTION
Numerous microfluidic devices have been designed for generating concentration gradients and used to study cell chemotaxis. However, current devices suffer from several limitations, such as flow-associated shear stresses that perturbate cell, closed conduit configurations which entail developing new culturing protocols, and lack of real time control of gradient’s slope [1]. Here, we introduce a gradient formed in an open space using active flow, yet without shear, and which can be hydrodynamically positioned and reconfigured, thus defined as a floating gradients.

CONCEPT
Consider four apertures in a flat surface that are regularly arranged on the corners of a virtual square, with two opposing ones used for injection of chemicals, and the other two for aspiration. The injected chemicals are hydrodynamically deflected and confined if the aspiration flow rate markedly exceeds the injection flow rate. Dual injection (and aspiration) of chemicals leads to the formation of a stagnation point (SP) at the center of the surface as a result of the head-on configuration of the two microjets, Figure 1a. The microjets split at the SP and each half runs side-by-side with the opposing jet (forming an interface between both chemicals) toward the aspiration apertures. We designed a microfluidic probe (MFP) [2] with 4 apertures following this idea, which we call stagnation point MFP (SP-MFP), Figure 1b-c. The SP-MFP is made of Si chip and a PDMS interface which receives capillaries that are connected to syringe pumps. For operation, the SP-MFP is immersed in fluid and brought close to a planar substrate to form a narrow gap, Figure 1d.

Figure 1: Microfluidic stagnation point (SP) formed in the open space under a SP-MFP. (a) Schematic of the two injection and two aspiration apertures, and the generated SP as a consequence of the head-on geometry of the two microjets. (b) X-X’ and (c) Y-Y’ cross-sectional views of (a). (d) The SP-MFP is immersed in a liquid and aligned in parallel to a proximal transparent substrate by visualizing it with the inverted microscope. A SP-MFP with 360 µm wide apertures centered 500 µm from the center and a 50 µm gap were used for this study.
RESULTS AND DISCUSSION

There is no flow at the SP, and negligible shear stress in the immediate vicinity (not shown). As a result of molecular diffusion between both confined streams which acting as a source and sink, a stable gradient forms across the SP and along the interface, Figure 2a. The gradient’s slope can be adjusted rapidly by modulating the two aspiration flow rates only, Figure 2d.

Figure 2: Modulation of the gradient’s slope by adjusting the aspiration flow rates. Water with fluorescein and pure water are injected through the top right and bottom left apertures, respectively, and aspirated back in through the other two apertures. By keeping the injection flow rates constant (\(Q_{I1} = 10 \text{ nl/s}\)) and changing the aspiration flow rate (\(Q_{A1}\)) each time, the gradient’s length and slope angle were changed. (a) \(Q_{A1} = 20 \text{ nl/s} (Q_{A1}/Q_{I1} = 2)\). (b) \(Q_{A1} = 50 \text{ nl/s} (Q_{A1}/Q_{I1} = 5)\). (c) \(Q_{A1} = 200 \text{ nl/s} (Q_{A1}/Q_{I1} = 20)\). (d) Fluorescence intensity profiles of the generated gradients at different aspiration flow rates. Scale bar in the micrographs and their corresponding insets are 200 µm and 100 µm, respectively.

Moreover, we show that the SP can be displaced hydrodynamically, without physical movement of the SP-MFP, by adjusting the injection and/or aspiration flow rates to have each aperture with different flow rate; the SP moves towards apertures with lower flow rates, and thus allows positioning the gradient on demand, Figure 3. An oscillatory gradient can thus readily be produced by programming the syringe pumps accordingly. If the two aspiration flow rates are also changed simultaneously, the gradient slope can be varied concurrently. The SP-MFP thus allows generating a gradient floating between pairs of injected and immediately re-aspirated streams that can be dynamically modulated.

Figure 3. Hydrodynamic displacements of the stagnation point (SP) and gradients by adjusting the flow rates only. (a1-d1) The SP is centered between the four apertures and the gradient is formed along a straight interface when \(Q_{I1} = Q_{I2} = 10 \text{ nl/s}\) and \(Q_{A1} = Q_{A2} = 150 \text{ nl/s}\). (a2-d2) When different flow rates are used for each aperture, the SP moves and a curved interface is formed (\(Q_{I1} = 10, Q_{I2} = 70, Q_{A1} = 170,\) and \(Q_{A2} = 100\)). (a) 3D simulation streamlines of the flow showing the SP (pointed by the black arrow) when centered (a1) and when moved (a2). (b) Fluorescence micrograph of green and red tracer microbeads (2 µm in size) which were injected through one aperture each. The diverging streaklines (2s exposure time) reveal the SP (pointed by the white arrow) when centered (b1) and when moved (b2). (c) 3D simulation and (d) fluorescence micrographs of the generated gradients at the interface are shown when the interface is a straight line and centered (c1, d1) and when it is a curved line (c2, d2).
CONCLUSION

Using a SP-MFP, a floating gradient in (i) open space is (ii) formed which can be (iii) adjusted rapidly, (iv) yet is shear free, and can be moved by either (v) physically moving the SP-MFP, or by (vi) hydrodynamically moving the SP. The proposed approach overcomes limitations of previous gradient generators, and may open new avenues for biological studies, in particular of chemotaxis of sensitive cells such as primary neurons and stem cells.

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